Rationale for the Use of Linezolid (L) and Rifampicin (R) Combinations to Prevent Selection of Resistant *Staphylococcus aureus* Mutants: Multiple-dose Simulations Using an *in Vitro* Dynamic Model

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Background

- Based on our studies with L-exposed *S. aureus* in an *in vitro* dynamic model, anti-mutant ratios of the 24-hour area under the concentration-time curve (AUC) to the MIC may or may not be attainable at clinical doses [1].
- To explore if combinations of L with R are able to restrict *S. aureus* resistance, the enrichment of L- and R-resistant mutants was studied by simulating single (L or R) and combined (L+R) treatments at therapeutic and sub-therapeutic AUCs.

Materials/Methods

- A clinical isolate of *S. aureus* (MIC_L 2 mg/l; MIC_R 0.016 mg/l) enriched with its L-resistant mutant (MIC_L 8 mg/l [1]) was exposed to twice daily L or once-daily R, alone and in combination, in five-day treatments.
- Mono-exponential pharmacokinetic profiles of L with a half-life of 6 h [2] and R with a half-life of 3 h [3] were simulated at therapeutic AUCs (240 and 60 mg×h/l – regimens L240 and R60, respectively) and sub-therapeutic AUCs (120 and 15 and 30 mg×h/l – regimens L120, R15 and R30, respectively).
- Simulated combined treatments were L240+R15, L240+R30 and L240+R60 and L120+R15, L120+R30 and L120+R60.
- A previously described dynamic model [1] was used in simulations of single drug treatments with L and R. To simulate combination treatments, the model was modified according to the Blaser and Zinner principle [4] to provide simultaneous mono-exponential elimination of L and R.

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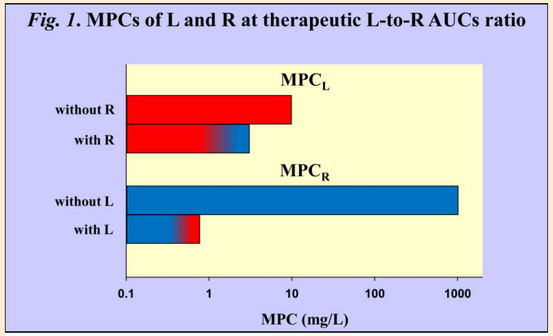
- The mutant prevention concentrations (MPCs) of L (MPC_L) and R (MPC_R) were determined for the single agents and their combinations. In the latter case L-to-R concentration ratios were chosen as AUC ratios used in pharmacokinetic simulations: 2:1 (L120+R60), 4:1 (L120+R30 and L240+R60), 8:1 (L120+R15 and L240+R30) and 16:1 (L240+R15).
- Time courses of resistant mutants were characterized by the area under the bacterial mutant concentration–time curve ($AUBC_M$ [5]) calculated from time zero to 120 h after the start of treatment and corrected for the area under the lower limit of detection over the same time interval.

Results

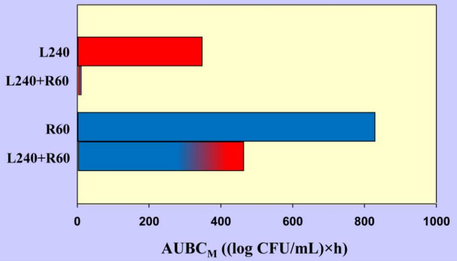
- Regardless of the L-to-R concentration ratio, the MPC_L determined in the presence of R was about 3-fold lower than without R (2.5-3.1 versus 10 mg/l). The MPC_Rs determined in the presence of L were 760-6400-fold lower than without L: 0.16-1.35 versus 1024 mg/l. The effects of R on the MPC_L and those of L on the MPC_R at the therapeutic L-to-R concentration ratio are demonstrated on Fig. 1.

***Fig. 1.* MPCs of L and R at therapeutic L-to-R AUCs ratio**



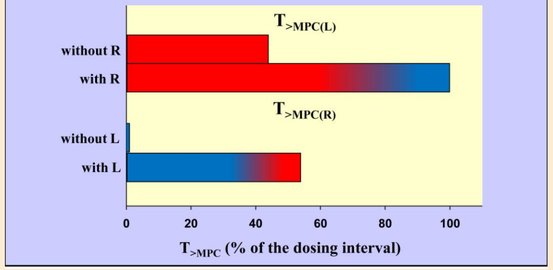
- *S. aureus* mutants resistant to 2× and 4×MIC of L and to 2×, 4×, 8× and 16×MIC of R were enriched in all single treatments whereas there was no enrichment of L-resistant mutants in combined treatments. Furthermore, using L+R combinations R-resistant mutants were not enriched during the treatments but they regrew subsequently.
- The described differences in mutant selection between mono- and combined treatments were reflected by the $AUBC_M$ parameter calculated for mutants resistant to 2×MIC of L or R (Fig. 2). As seen in the figure, under the influence of R the $AUBC_M$ for L-resistant mutants was reduced to zero. Under the influence of L the $AUBC_M$ for R-resistant mutants was reduced by 1.8 times..

***Fig. 2.* $AUBC_M$s in single and combined treatments with L and R (therapeutic dosing regiments)**



- The described differences in the $AUBC_M$ observed in single and combined treatments can be explained by the differences in T>MPC. As seen in Fig. 3, because of decreasing MPC_L in the presence of R, T>MPC for L in the combined treatment (regimen L240+R60) increased 2.3 times as compared to the T>MPC in a single treatment with L (100% of the dosing interval versus 44% in a single treatment).
- A similar increase in the T>MPC was observed with R: 54% of the dosing interval in the combined treatment versus 0% in the single treatment.

***Fig. 3.* $T_{>MPC}$s in single and combined treatments with L and R at therapeutic AUCs**



Conclusions

- Full suppression of L-resistant and the restriction of R-resistant *S. aureus* mutants exposed to L+R combinations were consistent with decreasing MPC_L and MPC_R.
- Determination of the MPC at pharmaco-kinetically-based antibiotic concentration ratios may be useful to predict *S. aureus* resistance in combined antibiotic treatments.

References:

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